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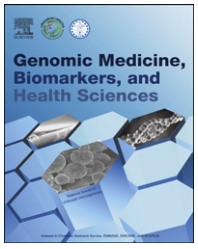

ORIGINAL ARTICLE

Malignant thymoma: Long-term outcomes with radiotherapy

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Abstract We analyzed the clinical outcome of stage II to IV malignant thymoma. This study focused on the treatment of 60 cases that combined surgery (biopsy or resection) and radiation therapy (with or without chemotherapy). Univariate and multivariate analyses of prognostic factors predicting survival were carried out. There is a statistically significant relationship between the extent of surgery and the local control (19.4% of relapse after complete resection vs. 41.2% of relapse after partial resection or biopsy, $p = 0.0001$). Mediastinal radiation dose ($\geq$50 Gy) had a significant effect in decreasing recurrence ($p = 0.0001$) and distant metastasis ($p = 0.011$). The rates of local recurrence (30%) and distant metastasis (25%) justify recommending a higher dose of mediastinal radiation ($\geq$50 Gy) for patients with malignant thymoma.

Introduction

Thymomas are the most common form of primary anterior mediastinal tumors and account for 15–20% of all mediastinal cases.[1] They are derived from thymic epithelial cells

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Table 1 Patient characteristics ($n = 60$).

Parameter	*n*	%
Age (y)		
<55	37	61.7
≥55	23	38.3
Sex		
Male	39	65
Female	21	35
Karnofsky score		
60	14	23.3
70	17	28.3
80	24	40
90	5	8.3
Systemic disease		
No	43	18
Yes	17	6
MG		
No	43	71.7
Yes	17	28.3
Tumor size (cm)		
≤5	9	15
>5, <8	35	58.3
≥8	16	26.7
Stage		
II	19	31.7
III	17	28.3
IV	24	40
Pathology		
Type A	4	6.7
Type AB	12	17
Type B1	6	6
Type B2	5	8.3
Type B3	8	13.3
Type C	25	41.7
Resectability		
Complete	31	51.7
Partial	9	15
Unresectable	20	33.3
OP way		
Biopsy	17	28.3
Sternectomy	31	51.7
VATS	12	20
RT dose (Gy)		
<50	15	25
≥50, <60	30	50
≥60	15	25
RT field		
Mediastinum	33	55
Mediastinum + SCV	27	45
SCV dose (Gy)		
<45	42	70
≥45	18	30
CT		
RT alone	46	76.7
RT + CT	14	23.3

CT = computed tomography; MG = myasthenia gravis; OP = operation; SCV = supraclavicular; RT = radiotherapy; VATS = video-assisted thoracic surgery.

and distinguished from thymic lymphomas, germ cell tumors, and carcinoid tumors.[2] Few thymomas are associated with as many paraneoplatic syndromes, including myasthenia gravis (MG), pure red cell aplasia, acquired hypogammaglobulinemia, and connective tissue disorders.[1,3] MG is, by far, the most common, being reported in 25–35% of patients with thymoma.[4]

Several studies have indicated the importance of initial tumor invasion and the extent of surgical resection as predictors of recurrence and survival after resection of a thymoma.[5–7] The most widely employed system for clinical staging at initial presentation is that proposed by Masaoka et al.[8]

Although most authors believe that tumor stage at initial presentation and the extent of surgical resection reliably predict thymoma prognosis, the findings have been equivocal when other predictors of prognosis are examined. The histologic classification of thymoma has remained a subject of controversy for many years.[9] In 1999, the World Health Organization (WHO) Consensus Committee published a histologic typing system of tumors of the thymus.[10] Thymomas are now stratified into six entities (types A, AB, B1, B2, B3, and C) on the basis of the morphology of epithelial cells and the lymphocyte/epithelial cell ratio.

Surgery remains the mainstay of treatment, and radiation and chemotherapy also have been applied widely as adjuvant and palliative procedures.[11,12] In this retrospective study, we report on the WHO histologic classification and its clinicopathologic relationship and prognostic relevance in a series of 60 nonmetastatic irradiated malignant thymomas at Kaohsiung Medical University Hospital in Taiwan between 1993 and 2007.

The aim of this study was to analyze the long-term survival and prognostic factors of patients with malignant thymoma treated by radiation therapy in the light of radiation dose and field.

Materials and methods

Study population

Between January 1991 and May 2005, we performed a retrospective analysis of clinical and histopathological data on patients radiated for malignant thymoma at our department. A total of 64 patients with malignant thymoma underwent mediastinum radiotherapy (RT) with or without supraclavicular radiation. Four patients were excluded due

to incomplete RT treatment (total dose <40 Gy) or lack of exact pathologic data. Sixty patients, consisting of 39 men and 21 women whose age ranged from 14 to 73 years (median age = 50.5 years), had sufficient files of exact clinical and pathologic data for the current study. The surgical–pathologic staging system proposed by Masaoka et al[8] was used to describe the invasion of the surrounding organs. Pathologic examination, based on the WHO classification system,[10] was performed by a single pathologist who reviewed the hematoxylin and eosin stained sections without information on the clinical data. Two cases were "combined thymoma," which consisted of one type B1 plus type B2 thymoma and one type B1 plus type B3 thymoma. We decided to use the major component of the tumor for the histologic diagnosis. These cases were one type B1 and one type B3. Final pathologic staging was decided using the Masaoka staging system. Tumor size was measured by the largest diameter of the tumor mass on computed tomography scan or the resected tumor specimen. MG was related to disease in 17 patients (28.3%). No patient underwent preoperative steroid therapy. The characteristics of the patients are shown in Table 1.

Radiation technique

All patients received RT, while 14 patients were treated by adjuvant chemotherapy. The irradiated volume of the mediastinum covered the thymic tumor bed with a 1.5- to 2-cm safe margin. RT was performed with a 6- or 10-MV linear accelerator (Varian, Connecticut, USA). The treatment volume was encompassed via anteroposterior opposing portals (equal weighting or anterior weighting 2/3 or 3/4) or a single anterior portal, anterior wedge pair portals, and reduced irradiation with spinal cord shielding was administered from 40 to 45 Gy. The median radiation dose to the mediastinum was 52 Gy (40–62.2 Gy). Supraclavicular radiation was performed in 27 patients via 6 MV photon with anterior portal (median dose = 45 Gy; range 40–60 Gy). The daily fraction was 1.8–2 Gy, 5 days a week.

Adjuvant chemotherapy

Adjuvant chemotherapy was performed in selected cases of patients with thymic carcinoma and/or stage III and IV not radically resected. We chose not to radically resect those tumors with wide involvement of great mediastinal vessels or other major structures, using clinical and radiological criteria and, in a few cases, even an invasive approach [video-assisted thoracic surgery (VATS) or anterior mediastinotomy]. The chemotherapy regimen was administered to 14 patients [ifosfamide, cisplatin, and etoposide (64); cisplatin, etoposide and paclitaxel (6/14); cyclophosphamide, pharmarubicin, and cisplatin (2/14)].

Follow-up for all patients was conducted until death or end of the study. The median follow-up period is 3.7 years (range 2.06–14.66 years). The response, recurrence, or distant metastasis was assessed by serial examinations including chest plain film, computed tomography scan, abdominal sonography, or bone scan. Survival time was estimated from the start of RT. Follow-up information with respect to survival was available in our study.

Statistical analysis

The linear regression model by Pearson was employed to identify the correlation between variables. A p value less than 0.05 was considered statistically significant.

Association between categorical variables was determined by using the t-test and chi-square test. The method of Kaplan–Meier was used for the analysis of overall survival and freedom from relapse (disease-free survival), and the log-rank test for comparisons of survival (age: <55 years, ≥55 years; sex; Karnofsky scale; Masaoka staging system: II, III, and IV; WHO histologic classification: A, AB, B1, B2, B3, and B3 versus C and others; tumor size; completeness of resection; surgery way; presence of MG or other systemic disease; dose and field of radiation; with and without chemotherapy) by SPSS for Windows (version 11.0.1). Significance was defined as $p < 0.05$. Deaths as a result of MG or unrelated disease were excluded.

Results

At the end of follow-up, 24 (40%) patients had died. The median overall survival period from start of RT was 3.7 years for all patients. The median disease-free survival period was 6.29 years from start of RT. The overall actuarial 5- and 10-year survival rate was 41.7% and 11.7%, respectively (Fig. 1).

The operative approach used was sternotomy in 31 (51.7%) patients and VATS in 12 (20%). No intraoperative or postoperative mortality occurred; five patients had postoperative complications: four chest pain and one dyspnea. The actuarial 5- and 10-year survival rate was 66.7% and 16.1% for patients who had radical resection, 22.2% and 22.2% for those who had incomplete resection, 5% and 0% for those who had biopsy, respectively. Patients who underwent radical resection showed a significantly higher survival rate than those who received incomplete resection or biopsy ($p = 0.0001$).

The invasive tumors was extended to pleura in 15 cases, to the pericardium in 22 cases, to the great vessels in 16 cases, to the lung in 24 cases, to the chest wall in six cases, and to the diaphragm in one case. Tumors with invasion to neighboring organ(s) were noted in 45 (75%) cases; type C was more invasive than types A, AB, B1, B2, and B3, and stage IV was more invasive than stages II and III, as shown in Table 2.

Of the 60 patients, 58 (97%) tolerated RT well and completed the course as scheduled except for one patient who had chest pain that interrupted treatment for 2 weeks and another patient who had fever and dysphagia and took rest for 1 and ½ weeks. The most common symptoms during RT courses were cough (35/60, 58%), dysphagia (31/60, 52%), dermatitis (14/60, 23%), chest pain (11/60, 18%), dyspnea (9/60, 15%), nausea (6/60, 10%), and fever (2/60, 3%). Four patients (7%) had radiation pneumonitis after completion of treatment, and symptoms were relieved after supportive treatment. Mediastinal RT was administered in 33 patients (55%), and mediastinum with supraclavicular RT was administered in 27 patients (45%). Mediastinum RT was more applied in stage IV (17/33, 50%), and mediastinum with supraclavicular RT was more applied

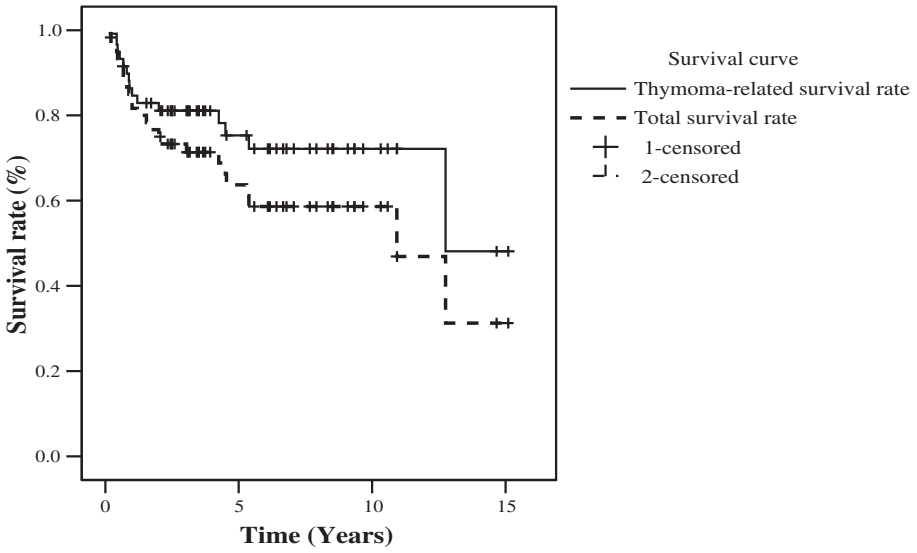

Figure 1 Survival curves for entire patient populations.

in stage II (12/27, 44%), with $p = 0.0273$. Comparison of mediastinal RT with mediastinum combined with supraclavicular RT yielded statistically significant results ($p = 0.0208$), as shown in Table 3.

Eighteen patients developed recurrence; unresectable and type C cases had higher recurrent rates. The relationship between histological subtypes, resectability, adjuvant chemotherapy, and recurrence is shown in Table 4. Fifteen patients developed distant metastasis: four had bone metastasis, three had brain metastasis, three had liver metastasis, one had pararenal metastasis, one had lung metastasis, one patient developed bone, liver, and lung metastases, one patient developed bone and brain metastases, and one patient developed bone and neck lymph node metastases.

Analysis of the prognostic value of various factors showed statistical significance as shown in Table 5. Prognostic factors were statistically significant including WHO histologic subtype, Masaoka clinical staging, Karnofsky score, surgery way, resectability, RT field, RT dose, RT fraction, and adjuvant chemotherapy. Mediastinal radiation dose ($\geq$50 Gy) had a significant effect in decreasing recurrence ($p = 0.0001$) and distant metastasis ($p = 0.011$). Mediastinum and supraclavicular fossa irradiation had a statistically significant impact in decreasing distant metastasis ($p = 0.0149$), but no statistically significant effect in recurrence ($p = 0.1492$).

Table 2 Histologic subtypes and the relationship with tumor invasion.

Histologic subtype	II	III	IV	Total	Cases of invasion to neighboring organ
A	2	0	2	4	2 (50%)
AB	7	3	2	12	6 (50%)
B1	3	2	1	6	4 (67%)
B2	2	1	2	5	3 (60%)
B3	3	2	3	8	6 (75%)
C	2	9	14	25	24 (96%)
Total	19	17	24	60	45 (75%)

Discussion

Several studies have been performed to identify the prognostic factors to program the most adequate therapeutic strategy for thymic epithelial tumors.[7,13–15] Surgery is the best treatment in patients with early stage of thymic epithelial tumors and leads to a good long-term survival.[7,13,14] In the advanced stages, a multidisciplinary approach is preferable, even if the prognosis seems to depend largely on the ability to perform a radical resection.

In a study conducted on a large number of patients, Regnard et al[13] identified the completeness of resection as the only significant independent prognostic factor at multivariate analysis and, on the basis of their results, they proposed to include this factor in a modified clinical–pathologic staging system of thymomas. In our experience, patients who underwent radical resection had a higher 5- and 10-year survival rate (66.7% and 16.1%) than patients who received incomplete resection (22.2% and 22.2%) or biopsy (5% and 0%). In addition, surgical approaches have evolved recently. We found that patients who underwent VATS had a better prognosis than those who had undergone sternectomy.

Regarding the surgical–pathologic staging system proposed by Masaoka et al, several authors agree that it is the best prognostic factor for thymic epithelial tumors predicting long-term survival.[6–8,16,17] We confirm this thesis because, in our series, we found a significantly better survival rate in stage II than in stage III and IV cases (5-year survival: 63% and 22%, respectively, $p = 0.0001$).

Meanwhile, the prognostic relevance of histology is still under debate, due to the numerous histological classifications[4] that add to the confusion and make the analysis and comparison of various results difficult. In 1999, the WHO Consensus Committee published a new classification system regarding the criteria to distinguish the different thymic

Table 3 Comparison with mediastinum with or without supraclavicular RT.

	Mediastinum ($n = 33$)		Mediastinum and SCV ($n = 27$)		p
	n	%	n	%	
Pathology					
1	12	38.24	13	48.15	0.361
Others	21	61.76	14	51.85	
Stage					
II	7	20.59	12	44.44	0.0273
III	9	29.41	8	29.63	0.2565
IV	17	50	7	25.93	0.0292
Sex					
Female	10	32.35	11	40.74	0.5016
Male	23	67.65	16	59.26	
Karnofsky score					
60	11	35.29	3	11.11	0.1255
70	9	26.47	8	29.63	
80	9	26.47	15	55.56	
90	4	11.76	1	3.7	
Systemic disease					
Yes	8	23.53	9	33.33	0.4002
No	25	76.47	18	66.67	
Age (y)					
<55	21	64.71	16	59.26	0.6655
≥ 55	12	35.29	11	40.74	
MG					
No	12	35.29	5	18.52	0.15
Yes	21	64.71	22	81.48	
Tumor size (cm)					
≤ 5	4	11.76	5	18.52	0.5379
>5, <8	20	58.82	15	55.56	
≥ 8	9	29.41	7	25.93	
Resectability					
Complete	16	50	15	55.56	0.2959
Partial	3	8.82	6	22.22	
Unresectable	14	41.18	6	22.22	
OP way					
No	10	29.41	7	25.93	0.6505
Sternectomy	17	52.94	14	51.85	
VATS	6	17.65	6	22.22	
RT dose (Gy)					
<50	13	41.18	2	7.41	0.0208
≥ 50, <60	13	38.24	17	62.96	0.832
≥ 60	7	20.59	8	29.63	0.0232
RT fraction					
≤ 25	10	32.35	2	7.41	0.0191
>25	23	67.65	25	92.59	

MG = myasthenia gravis; OP = operation; SCV = supraclavicular; RT = radiotherapy; VATS = video-assisted thoracic surgery.

epithelial tumors.[10] This system classifies thymic epithelial tumors into six subtypes: A, AB, B1—B3, and C. At present, only few papers have tested the prognostic and clinical validity of the new WHO classification.[16—18] Okumura et al reviewed 273 cases of thymic epithelial tumors and classified them according to the WHO system. Their study suggested that subtypes B2 and B3 tumors had a more malignant behavior in terms of postoperative survival,

Table 4 Histologic subtypes and the relationship with resectability and recurrence.

Histologic subtype	Resection			Recurrence
	Complete	Subtotal resection	Biopsy	
A ($n = 4$)	2	0	2	2
AB ($n = 12$)	8	4	0	3
B1 ($n = 5$)	4	0	2	2
B2 ($n = 5$)	4	0	1	2
B3 ($n = 8$)	5	1	2	1
C ($n = 25$)	8	4	13	8
Total	31 (41.4%)	9 (10.5%)	20 (35.1%)	18

invasiveness, and tumor recurrence, compared with subtypes A, AB, and B1. In this study, we did not find any correlation between subtypes A, AB, and B1—B3 and the risk of aggressiveness (Table 6). When we compared subtypes A, AB, and B1—B3 with subtype C, the survival rate reached a statistically significant difference ($p = 0.0003$). Type C had a more invasive oncological behavior than subtypes A, AB, and B1—B3. The 5- and 10-year survival rate was 41.7% and 11.7% in type C and 41.7% and 11.7% in subtypes A, AB, B1—B3.

Another therapeutic issue is the use of RT with or without chemotherapy. In tumors involving the surrounding structures, a radical resection is not always possible and a multidisciplinary approach is required; however, there is

Table 5 Variables analysis of survival, recurrence, and distant metastasis in malignant thymoma.

	Total	Death ($n = 24$)		Recurrence ($n = 18$)		Distant metastasis ($n = 15$)	
		n	p^*	n	p^*	n	p^*
Pathology							
1	25	15	0.0003	8	0.0185	9	0.0055
Others	35	9		10		6	
Stage							
II	19	1	0.0001	2	0.0008	0	0.0001
III	17	6		4		2	
IV	24	17		12		12	
Sex							
Female	21	8	0.6496			2	0.21
Male	39	16				13	
Karnofsky score							
60	14	12	0.0001	8	0.0009	8	0.0003
70	17	6		5		4	
80	24	6		5		3	
90	5	0		0		0	
Systemic disease							
No	43	18	0.9117	14	0.8253	11	0.7243
Yes	17	6		4		4	
Age (y)							
<55	37	13	0.1319	12	0.4394	8	0.1495
≥ 55	23	11		6		7	
MG							
No	43	18	0.329	12	0.8848	12	0.2204
Yes	17	6		6		3	
Tumor size (cm)							
≤ 5	9	0	0.1026	2	0.8674	1	0.5039
>5, <8	35	16		9		10	
≥ 8	16	8		7		4	
Resectability							
Complete	31	4	0.0001	6	0.0001	2	0.0001
Partial	9	4		4		1	
Unresectable	20	16		8		12	
OP way							
Biopsy	17	12	0.0001	6	0.0014	8	0.0001
Sternectomy	31	11		11		6	
VATS	12	1		1		1	

Table 5 (*continued*).

	Total	Death ($n = 24$)		Recurrence ($n = 18$)		Distant metastasis ($n = 15$)	
		n	*p**	*n*	*p**	*n*	*p**
RT dose (Gy)							
<50	15	14	0.0001	11	0.0001	7	0.011
≥50, <60	30	6		5		4	
≥60	15	4		2		4	
RT fraction							
≤25	12	10	0.0007	9	0.0001	6	0.0091
>25	48	14		9		9	
RT field							
Mediastinum	33	18	0.0372	13	0.1492	13	0.0149
Mediastinum + SCV	27	6		5		2	
SCV dose (Gy)							
<45	42	20	0.0711	14	0.2351	15	0.0063
≥45	18	4		4		0	
CT							
RT alone	46	15	0.0048	10	0.0001	8	0.3787
RT + CT	14	9		8		7	

**p* value: value of log rank for survival.
CT = computed tomography; MG = myasthenia gravis; OP = operation; SCV = supraclavicular; RT = radiotherapy; VATS = video-assisted thoracic surgery.

Table 6 The relationships between pathology and prognosis of malignant thymoma.

Pathology		Death ($n = 9$)		Recurrence ($n = 10$)		Distant metastasis ($n = 6$)	
		n	*p*	*n*	*p*	*n*	*p*
Type A	4	2	0.1556	2	0.1196	2	0.1395
Type AB	12	1		3		2	
Type B1	6	2		2		1	
Type B2	5	2		2		1	
Type B3	8	2		1		0	

no common agreement about the sequence of different therapeutic options.

Unfortunately, our study is not a prospective study and covers a long period of time. Adjuvant chemotherapy was performed in selected cases of patients with type C and/or stage III and IV not radically resected. Other experiences showed that neoadjuvant chemotherapy could improve the resectability of thymic epithelial tumors or, at least, make the resection easier, reducing the bulk of tumor and the vascular or mediastinal infiltration.[19,20] The results of 14 patients who received adjuvant chemotherapy showed no benefit in prognosis.

In conclusion, RT plays a part in the multimodality therapy of malignant thymoma. Our study showed that high radiation dose (more than 50 Gy) had significantly increased survival overall ($p = 0.0001$) and decreased distant metastasis ($p = 0.011$).

Further and broader studies are needed in order to verify the utility of prognostic factors in clinical practice and to improve the therapeutic strategies for patients with malignant thymomas.

Acknowledgments

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